electrode **35**, or (**20A**) in contact with the first microchannel **15**. Figure 1B depicts a cell handling module **40** and a second storage well **25A** with a microchannel **20** to the cell handling module **40**. For example, the cell handling module **40** could be a cell lysis module and the storage well **25A** could contain lysis reagents. Figure 1C depicts acell handling module **40** that is a cell capture or enrichment module, with an additional reagent storage well **25B** for elution buffer. Figure 1D depicts the addition of a reaction module **45**, with a storage module **25C**, for example for storage of amplification reagents. Optional waste module **26** is connected to the reaction module **45** via a microchannel **27**. All of these embodiments may additionally comprise valves, waste wells, and pumps, including additional electrodes.

A1

Please insert the following paragraph beginning at page 2, line 17, with the following paragraph:

Figure 2 depicts some preferred embodiments for the modules of the invention. Figure 2A depicts a preferred embodiment wherein the cell handling module is a cell lysis module **50**. Figure 2B depicts a preferred embodiment wherein the cell handling module is a cell removal module **60**. Figure 2C depicts a preferred embodiment wherein the cell handling module is a cell concentration module **70**. Figure 2D depicts a preferred embodiment wherein the cell handling module is a cell separation module **80**. Figure 2E depicts a preferred embodiment wherein the cell separation module is an electrophoresis module **90**. Figure 2F depicts a preferred embodiment wherein the reaction module is a nucleic acid amplification module **100**. Figure 2G depicts a preferred embodiment wherein the reaction module includes a thermal module **110**. Figure 2H depicts a pump **120** and a valve **130**.

A2

Please replace the paragraph beginning at line 9 of page 10 with the following rewritten pargarph:

In addition to the flow channel system, the devices of the invention are configured to include one or more of a variety of components, herein referred to as "modules", that will be present on any given device depending on its use. As shown in Figures 2A-2H, these modules include, but are not limited to: sample inlet ports; sample introduction or collection modules; cell handling modules **40** (for example, for cell lysis, cell removal, cell concentration, cell separation or capture, cell growth, etc.); separation modules, for example,

A3

for electrophoresis, dielectrophoresis, gel filtration, ion exchange/affinity chromatography (capture and release) etc.; reaction modules **45** for chemical or biological alteration of the sample, including amplification of the target analyte (for example, when the target analyte is nucleic acid, amplification techniques are useful, including, but not limited to polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), and nucleic acid sequence based amplification (NASBA)), chemical, physical or enzymatic cleavage or alteration of the target analyte, or chemical modification of the target; fluid pumps **120**; fluid valves **130**; thermal modules **110** for heating and cooling; storage modules for assay reagents; mixing chambers; and detection modules.

Please replace the paragraph beginning at line 29 of page 10 with the following rewritten paragraph:

In a preferred embodiment, the devices of the invention include a cell handling module **40** (Figure 1B and 1C). This is of particular use when the sample comprises cells that either contain the target analyte or that must be removed in order to detect the target analyte. Thus, for example, the detection of particular antibodies in blood can require the removal of the blood cells for efficient analysis, or the cells (and/or nucleus) must be lysed prior to detection. In this context, "cells" include eukaryotic and prokaryotic cells, and viral particles that may require treatment prior to analysis, such as the release of nucleic acid from a viral particle prior to detection of target sequences. In addition, cell handling modules may also utilize a downstream means for determining the presence or absence of cells. Suitable cell handling modules include, but are not limited to, cell lysis modules **50** (Figure 2A), cell removal modules **60** (Figure 2B), cell concentration modules **70** (Figure 2C), and cell separation or capture modules **80** (Figure 2D). In addition, as for all the modules of the invention, the cell handling module is in fluid communication via a flow channel with at least one other module of the invention.

Please replace the paragraph beginning at line 8 of page 11 with the following rewritten paragraph:

In a preferred embodiment, the cell handling module **40** includes a cell lysis module **50** (Figure 2A). As is known in the art, cells may be lysed in a variety of ways, depending on

the cell type. In one embodiment, as described in EP 0 637 998 B1 and U.S. Patent No. 5,635,358, hereby incorporated by reference, the cell lysis module may comprise cell membrane piercing protrusions that extend from a surface of the cell handling module. As fluid is forced through the device, the cells are ruptured. Similarly, this may be accomplished using sharp edged particles trapped within the cell handling region. Alternatively, the cell lysis module can comprise a region of restricted cross-sectional dimension, which results in cell lysis upon pressure.

Please replace the paragraph beginning at line 26 of page 11 with the following rewritten paragraph:

In a preferred embodiment, the cell handling module **40** includes a cell separation or capture module **80** (Figure 2D). This embodiment utilizes a cell capture region comprising binding sites capable of reversibly binding a cell surface molecule to enable the selective isolation (or removal) of a particular type of cell from the sample population, for example, white blood cells for the analysis of chromosomal nucleic acid, or subsets of white blood cells. These binding moieties may be immobilized either on the surface of the module or on a particle trapped within the module (i.e. a bead) by physical absorption or by covalent attachment. Suitable binding moieties will depend on the cell type to be isolated or removed, and generally includes antibodies and other binding ligands, such as ligands for cell surface receptors, etc. Thus, a particular cell type may be removed from a sample prior to further handling, or the assay is designed to specifically bind the desired cell type, wash away the non-desirable cell types, followed by either release of the bound cells by the addition of reagents or solvents, physical removal (i.e. higher flow rates or pressures), or even in situ lysis.

Please replace the paragraph beginning at line 8 of page 12 with the following rewritten paragraph:

In a preferred embodiment, the cell handling module **40** includes a cell removal module **60**(Figure 2B). This may be used when the sample contains cells that are not required in the assay or are undesirable. Generally, cell removal will be done on the basis of

a7

size exclusion as for "sieving", above, with channels exiting the cell handling module that are too small for the cells.

Please replace the paragraph beginning at line 12 of page 12 with the following rewritten paragraph:

a8

In a preferred embodiment, the cell handling module **40** includes a cell concentration module **70** (Figure 2C). As will be appreciated by those in the art, this is done using "sieving" methods, for example to concentrate the cells from a large volume of sample fluid prior to lysis.

Please replace the paragraph beginning at line 24 of page 14 has been amended as follows:

a9

In a preferred embodiment, the separation module **80** includes an electrophoresis module **90** (Figure 2E), as is generally described in U.S. Patent Nos. 5,770,029; 5,126,022; 5,631,337; 5,569,364; 5,750,015, and 5,135,627, all of which are hereby incorporated by reference. In electrophoresis, molecules are primarily separated by different electrophoretic mobilities caused by their different molecular size, shape and/or charge. Microcapillary tubes have recently been used for use in microcapillary gel electrophoresis (high performance capillary electrophoresis (HPCE)). One advantage of HPCE is that the heat resulting from the applied electric field is efficiently dissipated due to the high surface area, thus allowing fast separation. The electrophoresis module serves to separate sample components by the application of an electric field, with the movement of the sample components being due either to their charge or, depending on the surface chemistry of the microchannel, bulk fluid flow as a result of electroosmotic flow (EOF).

Please replace the paragraph beginning at line24 of page 15 with the following rewritten paragraph:

a10

In a preferred embodiment, the devices of the invention include a reaction module **45** (Figure 1D). This can include either physical, chemical or biological alteration of one or more sample components. Alternatively, it may include a reaction module wherein the target analyte alters a second moiety that can then be detected; for example, if the target analyte is an enzyme, the reaction chamber may comprise an enzyme substrate that upon modification

by the target analyte, can then be detected. In this embodiment, the reaction module may contain the necessary reagents, or they may be stored in a storage module and pumped as outlined herein to the reaction module as needed.

Please replace the paragraph beginning at line 24 of page 16 with the following rewritten paragraph:

A10

In a preferred embodiment, the reaction module **45** includes a chamber for the biological alteration of all or part of the sample. For example, enzymatic processes including nucleic acid amplification **100** (Figure 2F), hydrolysis of sample components or the hydrolysis of substrates by a target enzyme, the addition or removal of detectable labels, the addition or removal of phosphate groups, etc.

Please replace the paragraph beginning at line 16 of page 38 with the following rewritten paragraph:

Sub C3

A11

In this and other embodiments, a thermal module **110** (Figure 2G) may be used, that is either part of the reaction chamber **45** or separate but can be brought into spatial proximity to the reaction module. The thermal module **110** can include both heating and/or cooling capability. Suitable thermal modules are described in U.S. Patent Nos. 5,498,392 and 5,587,128, and WO 97/16561, incorporated by reference, and may comprise electrical resistance heaters, pulsed lasers or other sources of electromagnetic energy directed to the reaction chamber. It should also be noted that when heating elements are used, it may be desirable to have the reaction chamber be relatively shallow, to facilitate heat transfer; see U.S. Patent No. 5,587,128.

Please replace the paragraph beginning at line1, page 39 with the following rewritten paragraph:

A12

In a preferred embodiment, the devices of the invention include at least one fluid pump **120** (Figure 2H). Pumps generally fall into two categories: “on chip” and “off chip”; that is, the pumps (generally electrode based pumps) can be contained within the device itself, or they can be contained on an apparatus into which the device fits, such that alignment occurs of the required flow channels to allow pumping of fluids.

Please replace the paragraph beginning at line 5 of page 39 with the following rewritten paragraph:

Sub C2

213

In a preferred embodiment, the pumps **120** (Figure 2H) are contained on the device itself. These pumps **120** are generally electrode based pumps; that is, the application of electric fields can be used to move both charged particles and bulk solvent, depending on the composition of the sample and of the device. Suitable on chip pumps include, but are not limited to, electroosmotic (EO) pumps and electrohydrodynamic (EHD) pumps; these electrode based pumps have sometimes been referred to in the art as "electrokinetic (EK) pumps". All of these pumps rely on configurations of electrodes placed along a flow channel to result in the pumping of the fluids comprising the sample components. As is described in the art, the configurations for each of these electrode based pumps are slightly different; for example, the effectiveness of an EHD pump depends on the spacing between the two electrodes, with the closer together they are, the smaller the voltage required to be applied to effect fluid flow. Alternatively, for EO pumps, the spacing between the electrodes should be larger, with up to one-half the length of the channel in which fluids are being moved, since the electrode are only involved in applying force, and not, as in EHD, in creating charges on which the force will act.

Please replace the paragraph beginning at line 28 of page 40 with the following rewritten paragraph:

Sub C5

314

In a preferred embodiment, the devices of the invention include at least one fluid valve **130** (Figure 2H) that can control the flow of fluid into or out of a module of the device, or divert the flow into one or more channels. A variety of valves are known in the art. For example, in one embodiment, the valve may comprise a capillary barrier, as generally described in PCT US97/07880, incorporated by reference. In this embodiment, the channel opens into a larger space designed to favor the formation of an energy minimizing liquid surface such as a meniscus at the opening. Preferably, capillary barriers include a dam that raises the vertical height of the channel immediately before the opening into a larger space such a chamber. In addition, as described in U.S. Patent No. 5,858,195, incorporated herein by reference, a type of "virtual valve" can be used.